Investing To Meet The Scientific Challenges Of HIV/AIDS

The world must fund a robust research agenda on everything from curative therapies to vaccines and other new prevention tools.

by Anthony S. Fauci and Gregory K. Folkers

ABSTRACT: Despite extraordinary scientific advances over more than twenty-five years, the human immunodeficiency virus (HIV) continues to exact an enormous toll worldwide. Given the limitations of current HIV treatment and prevention interventions and the financial and logistical impediments to delivering them, new and potentially transforming interventions are needed if the HIV/AIDS pandemic is to be significantly slowed. Serious scientific challenges remain in the realm of developing potentially curative therapies and a safe and effective HIV vaccine, and in developing, assessing, and validating other new prevention modalities. Substantial funding of the research enterprise must be maintained. [Health Aff (Millwood). 2009;28(6):1629–41]

THE PANDEMIC OF HUMAN IMMUNODEFICIENCY virus (HIV) infection—the cause of the acquired immune deficiency syndrome (AIDS)—has claimed more than twenty-five million lives and ranks among the most devastating scourges in human history. By any measure, HIV/AIDS belongs in the company of plagues such as the Black Death of the fourteenth century; the many epidemics of smallpox throughout history; the influenza pandemic of 1918–19; and the ongoing pandemics of two ancient diseases, tuberculosis and malaria.

Globally, HIV/AIDS has grown from a handful of reported cases in 1981 to a global pandemic that has affected virtually every country in the world.[1] Although prevalence of HIV infection has stabilized in recent years at some thirty-three million individuals, the burden of disease and the annual number of new infections remain high. Approximately 2.7 million people were infected in 2007 alone—an average of 7,400 people each day.[2] These enormous and unacceptable figures reflect the fact that despite much progress, a minority of people worldwide at risk of HIV infection has access to HIV prevention services that are proven to be effec-

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tive.[2, 3] HIV/AIDS has destroyed the health of individuals and the well-being of families and communities. It also threatens the economies of entire nations, especially in the developing world. In the United States, nearly 600,000 people have died of HIV/AIDS, and another approximately 1.1 million people are living with HIV infection.[4–6] Approximately 56,000 people in the United States have been infected with HIV each year for roughly the past fifteen years.

The catastrophe of HIV/AIDS has been tempered by many extraordinary successes, both in the realm of biomedical research and in delivering the fruits of that research to HIV-infected people. Of particular importance have been the development of antiretroviral drugs that can limit HIV's ability to replicate itself in the body and mitigate the consequent immune system damage. Also critical has been the formulation of strategies and clinical guidelines for the optimal use of these medications. Combination therapy with multiple antiretroviral drugs has resulted in dramatic reductions in AIDS-related illness and death wherever the medications have been available and appropriately used, in rich and poor countries alike.[2, 3]

Globally, about four million HIV-infected people in low- and middle-income countries are receiving antiretroviral drugs, up from about 400,000 at the end of 2003.[3] However, barriers to access to these drugs persist throughout the world, especially in developing countries, where only about 42 percent of those with advanced HIV disease who need antiretroviral therapy are receiving it. In addition, for every person put on antiretroviral therapy, two to three people are newly infected with HIV. At least at present, antiretroviral therapy is a lifelong commitment. It is extremely unlikely that we will have the logistical or financial capacity to reach and treat—indefinitely—everyone who requires antiretroviral therapy.

Even if access to proven tools of HIV prevention and treatment services were greatly improved by increased funding or improved efficiencies, slowing and ultimately ending the HIV/AIDS pandemic are also likely to require major advances in two areas. These are, first, curing a sizable proportion of those already infected with the virus such that lifelong therapy will not be required; and, second, developing more powerful tools of prevention to slow the onslaught of new infections. The scientific challenges related to these two goals are the most important issues in HIV/AIDS research today.

Toward A Cure For HIV Infection

Despite our considerable success in medically managing HIV infection and improving the length and quality of life of people living with HIV, there is no well-documented case of anyone being truly "cured" of HIV infection.[7] A true cure

would mean that someone in whom infection had been previously established no longer had HIV present anywhere in his or her body as a result of therapy. The reason no cure has occurred or been found is that HIV is unlike virtually any other virus in its ability to hide from the immune system and to be shielded from drug therapy in protected cellular sanctuaries referred to as latent "reservoirs" of virus.[8] These latent reservoirs are established within days of infection. The most potent combinations of anti-HIV drugs are unable to purge the virus from these hiding places—even in people who have received therapy for a decade or more. If therapy is discontinued in an HIV-infected person whose virus has been suppressed by such therapy, the virus hiding in these latent reservoirs almost invariably emerges from its slumber and begins replicating vigorously.

The best hope of eradicating HIV from its reservoirs may be the diagnosis and aggressive treatment of patients very early in the course of infection, before the reservoirs have become extensive. Recent studies have shown a steady and sharp decay (without elimination) of latent reservoirs in individuals treated aggressively with antiretroviral drugs within the first months of infection.[9] Treating even earlier in infection—before viral reservoirs are established—would be preferable. Experiments in animals and two decades of clinical experience treating humans demonstrate that giving antiretroviral drugs within forty-eight hours after exposure to HIV—a strategy called "post-exposure prophylaxis"—reduces the likelihood of HIV infection. However, only an extremely small fraction of HIV-infected people are identified in the very first days following exposure, and most of those reside in resource-rich settings.

■ **First indications.** The first clinical indications of HIV infection—the flu-like signs and symptoms that characterize the "acute HIV syndrome"—usually occur three to six weeks after exposure. Unfortunately, many of the early pathogenic events that largely determine the course of HIV infection already have occurred by the time the acute syndrome is recognized.[10]

Our current understanding is that a massive burst of HIV replication occurs soon after infection. This leads to the destruction of a substantial proportion of a person's CD4+ T cells, which are white blood cells crucial to maintaining the functioning of the human immune system. The burst of viral replication also leads to the spread of virus throughout the body and the "seeding" of the virus in various organs, particularly the lymphoid organs. Such organs include lymph nodes, the spleen, and other tissues that act as the body's filtering system, trapping invaders and presenting them to squadrons of immune cells that congregate there. Of particular importance are the billions of CD4+ T cells that reside in the gut. These are favorite targets of HIV infection during the early course of HIV disease, and it is likely that they sustain the most damage in acute infection.

■ **Immune response.** Following HIV infection, most people mount a vigorous immune response that dramatically reduces HIV replication and the levels of virus detectable in the blood. A person's peripheral blood CD4+ T-cell count, originally

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dramatically suppressed by the virus, often rebounds somewhat and may even approach its original level. Despite the body's aggressive immune responses, which are sufficient to clear most other viral infections, some HIV invariably escapes elimination. This is due in large part to the high rate of mutations that occur during the process of HIV replication, as well as to the HIV-mediated depletion or dysfunction of key immune-system components that otherwise might help clear the virus.

■ **Latent viral reservoir.** Some of the virus takes up residence in resting CD4+ T cells as inactive viral DNA (so-called provirus), integrated into the DNA of chromosomes of the host cell. Because the antiretroviral medications in our therapeutic arsenal attack actively replicating virus, they are not effective against hidden, inactive viral DNA. Even though highly potent combinations of antiretroviral drugs, when properly administered, usually suppress HIV to levels that are undetectable as free virus in the blood, the pool of latently infected cells persists. These reservoirs of HIV- infected cells probably exist in multiple locations, including the lymphoid tissue, circulating lymphoid cells, the brain, and perhaps in yet-to-be identified locations as well.

Over the past several years, numerous attempts have been made to eliminate the latent viral reservoir using agents that stimulate resting CD4+ T cells during the course of antiretroviral therapy, rendering the virus active and thus susceptible to the drugs. However, such attempts have been unsuccessful.[7] In addition, although an extremely small pool of truly resting, latently infected cells exists at any given point in time, this pool is continually being activated and replenished by ongoing low levels of virus replication in the absence of detectable virus in the bloodstream.[11]

■ **Key research challenges.** These persistent reservoirs of infected cells are major obstacles to the goal of a cure for HIV infection. Key research challenges include the following: (1) developing new tools for studying HIV latency; (2) determining the precise mechanisms of HIV persistence in known viral reservoirs, including resting CD4+ T cells; (3) identifying new viral reservoirs and how they form and are maintained; (4) determining the mechanisms and extent of the low-level viral replication seen in patients with well-controlled HIV infection; and (5) developing approaches to reactivating and eradicating latent HIV infection.

A cure theoretically could involve either complete eradication of HIV from the body—referred to as a true "sterilizing cure." Alternatively, a cure could translate into the shrinkage of HIV reservoirs, to the point where rebound of virus replication and the appearance of virus in the bloodstream do not occur even after the cessation of antiretroviral therapy—a "functional" cure.[7] A functional cure is probably most feasible in people treated early and aggressively for HIV infection.

This is because these individuals are most likely to have well-preserved HIV-specific immune responses essential for suppression of the reactivation of viral reservoirs following cessation of antiretroviral therapy.

For people treated later in the course of disease, novel approaches such as gene therapy may have a role. One HIV-infected person with acute myeloid leukemia, who received a stem cell transplant from another person carrying a gene that confers resistance to HIV infection (called a CCR5-Delta32), has remained free of detectable HIV for more than twenty months without undergoing any antiretroviral therapy.[12] Although stem cell transplants from donors who are genetically resistant to HIV infection do not have immediate, practical application as HIV therapy—because of their expense, their risk, and the difficulty in finding appropriate donors—this study is an encouraging "proof of concept" that a cure may be possible.

■ **Impact of a cure.** The impact of an HIV cure would be profound for individuals and communities, especially if a regimen were found that was relatively cheap and easily administered in resource-poor settings. Individuals would be spared the effects of the virus and the toxicities of therapy. The cost of lifetime treatment for HIV infection was recently estimated to be around US$1,100 annually in a resource-poor setting when antiretroviral therapy is initiated at a CD4+ T-cell count of higher than 250/mm^3.[13] Without the need to fund lifetime antiretroviral therapy for an ever-increasing number of HIV-infected people, resources would be freed for other health-related services. These could include not only HIV testing and prevention but also the training of health workers and ancillary personnel, support of orphans and vulnerable children, and the strengthening of health care systems and infrastructure.

New And Improved HIV Prevention Modalities

Important successes in HIV prevention have been achieved with the following proven strategies: (1) HIV testing and counseling; (2) mass-media campaigns; (3) education and behavior modification; (4) condoms (male and female); (5) screening of blood supplies; (6) treatment and prevention of drug and alcohol abuse; (7) clean needles and syringes (that is, "needle exchange" programs); (8) antiretroviral therapy for interruption of HIV transmission from mother to child; (9) antiretroviral therapy for postexposure prophylaxis; and (10) medically supervised adult male circumcision. Prevention programs must be dramatically "scaled up"—and in some cases refined and improved—if the staggering number of new HIV infections is to be reduced.[3,14]

However, to implement a truly transformative HIV prevention effort, new prevention modalities are needed. Especially critical will be those that rely less directly on a person's decisions at the time of potentially risky sexual or drug-taking behavior (for example, the use of condoms) and more on a biological "backstop" of protection that is in place prior to activities that put a person at risk of HIV

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infection.

Several of the most compelling challenges in HIV/AIDS research today relate to the development and scientific assessment and validation of new approaches to blocking HIV transmission.[3,14,15] These approaches may reduce the likelihood that infected people will transmit HIV to others, or help protect an uninfected person from acquiring HIV. Some have the potential to do both.

■ **Reducing transmission by reducing viral load.** In a majority of HIV-infected individuals, proper administration of combination antiretroviral therapy can reduce virus in the fluid portion of the blood to extremely low levels, benefiting their health and making them less likely to transmit the virus.

Compelling evidence that reducing viral load can reduce transmission comes from studies of maternal-fetal transmission. The relationship between viral load and transmissibility also has been demonstrated in relation to sexual transmission. Studies of monogamous, HIV-"serodiscordant" couples, in which one person is HIV-infected and the other is not, have shown a direct correlation between the infected partner's viral load and the probability of transmission to the uninfected partner.[16] At a population level, longitudinal measurements recently showed that lowering community viral load was correlated with a reduction in the HIV incidence rate in an inner-city community in Vancouver, British Columbia.[17]

Thus, given the effect of antiretroviral therapy on reducing viral load, and the relationship between viral load and the efficiency of transmission of HIV, it is reasonable to consider using treatment of HIV-infected individuals as a means of preventing HIV transmission. A recent modeling study provides the theoretical basis for a new, bold, but potentially important public health strategy.[18] The model predicts that within ten years of implementation, a program of universal, voluntary, annual HIV testing and immediate treatment of those who test positive could reduce HIV incidence from twenty new infections per thousand people per year—the current rate in high-prevalence countries such as South Africa—to less than one infection per thousand people per year. Furthermore, the model predicts that this strategy, referred to as "test and treat," could essentially end the pandemic within fifty years and thus could have a transformational effect on public health.

However, this potentially high-impact approach is based on a number of assumptions that will require validation before it can be translated into a public health policy. It is critical to pursue a research agenda that includes studies of feasibility, efficacy, the benefits to individual patients versus the benefits to society, and cost-effectiveness.[19]

■ **Pre-exposure prophylaxis with antiretroviral drugs.** Administering antiretroviral therapy to uninfected individuals at risk for HIV infection also holds

promise as an HIV prevention modality.[14, 15] This approach, referred to as "pre-exposure prophylaxis," is a well-established tool for preventing other infectious diseases, such as using antibiotics to prevent meningococcal infection in close contacts of a patient with invasive meningococcal disease. Theoretically, if HIV replication could be inhibited immediately following exposure to the virus, permanent infection might be avoided. Pre-exposure prophylaxis is especially promising because of its probable acceptability—it inhibits HIV without requiring changes in sexual habits. A successful pre-exposure prophylaxis regimen could be used by women and other vulnerable individuals without the consent or knowledge of their sexual partners.

Several lines of evidence suggest that pre-exposure prophylaxis against HIV infection could be feasible. For example, as noted above, antiretroviral drugs have been used with great success to prevent transmission of HIV from mother to infant. Numerous studies involving monkeys have shown that pre-exposure dosing with the antiretroviral drug tenofovir—with or without another antiretroviral drug, emtricitabine—can prevent infection with simian immunodeficiency virus, a pathogen closely related to HIV. Tenofovir and emtricitabine have good safety profiles; in addition, drug levels persist for relatively long periods of time in the body, which suggests that some protection may be afforded even if some doses are missed.

At least seven clinical trials of pre-exposure prophylaxis are under way and will provide important data on safety and efficacy, the development of HIV drug resistance, and the potential for increases in risky sexual behavior.[14] It also remains to be seen if pre-exposure prophylaxis regimens are cost-effective—a practical and ethical concern in a world where people already infected with HIV need antiretroviral therapy for their declining health and are unable to obtain it.

■ **Topical microbicides**. Topical microbicides are compounds formulated in gels, creams, films, vaginal rings, or other devices that are inserted into the vagina or rectum to reduce the likelihood that the user acquires HIV infection or other sexually transmitted infections during sexual intercourse.[20] A safe and effective topical microbicide would be an especially important method of prevention for women, who account for at least half of new HIV infections globally.[2] In many settings, women are now completely dependent on male-controlled modalities of protection, such as the male condom. The availability of effective topical microbicides would allow women to play a much more active role in the control of circumstances that might put them at risk of HIV infection. Microbicides also hold promise as a method of protecting receptive male partners during anal intercourse.

These products have varying mechanisms of action. However, they all focus on the earliest events that take place at and just below the mucosal surface in the setting of potential acquisition of HIV infection. Although there are relatively few cells susceptible to HIV on the outside layer of tissues of the vagina or rectum, the virus finds its way to a fertile region just below this layer, where large numbers of

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susceptible "target" cells—such as resting and activated CD4+ T cells—are found. HIV may reach these cells through breaks in the tissue caused by some microscopic injury or sexually transmitted diseases, by binding to a type of immune system cells known as dendritic cells that can ferry the virus to its target cells, or by other mechanisms yet to be elucidated. Candidate topical microbicides may serve as physical barriers, inhibit uptake by or infection of dendritic cells, neutralize or inhibit HIV at the mucosal surface, inhibit viral replication in infected cells, or enhance vaginal defenses (for example, by maintaining a pH that is inhospitable to HIV and other pathogens).

The field of microbicide research has not met with success thus far. Although most products have appeared safe in human trials, two compounds tested in large trials apparently increased the risk of infection.[12] Despite these setbacks, the microbicide field was encouraged in 2008 by a large clinical trial of a product called PRO 2000 that showed modest (30 percent) protective efficacy among women.[21] Although this result fell just short of statistical significance, it was the first indication that a microbicide to prevent HIV infection might actually work in people.

Definitive results are expected in late 2009 from a larger clinical trial of PRO 2000, and data continue to emerge from ongoing clinical trials with approximately ten other products.[14] These data, as well as ongoing basic research on the pathophysiology of the early events of HIV infection at mucosal surfaces, will help inform the way forward in this critical area of research.

■ **Preventing or treating co-infections.** Considerable epidemiologic evidence suggests a two-to-fivefold increased risk of acquiring HIV infection when another sexually transmitted infection is present.[22] One biologic explanation is the impaired integrity of the mucosa associated with certain sexually transmitted infections, such as genital infections caused by herpes simplex virus-2 (HSV-2). Additional mechanisms also may play a role and may help explain why even people with asymptomatic sexually transmitted infections, including non-ulcerative infections such as chlamydia and gonorrhea, also may be at increased risk of HIV infection.

Notably, immune cells activated by outside stimuli (such as infecting microbes) are particularly susceptible to HIV infection, even if the immune cells themselves are not infected by the other microbes and the mucosal surface is intact. Co-infections with sexually transmitted infections also may render an HIV-infected person more likely to transmit HIV to his or her sexual partner because such infections can increase the level of HIV in the blood and genital tract.

Data from modeling studies suggest that control of sexually transmitted infections could be a cost-effective HIV prevention measure in both early-phase and

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mature epidemics.[23] However, evidence from randomized controlled trials for this strategy is largely lacking, aside from a trial that showed a large effect of bacterial sexually transmitted infection control in the setting of an early-stage epidemic. Most recently, two large studies that examined suppression of the herpes simplex virus HSV-2, which causes genital herpes, with the drug acyclovir as a possible means of reducing the risk of HIV transmission did not yield a successful result.[24] However, because of the strong epidemiologic data linking sexually transmitted infections with HIV acquisition and transmission; the biologic plausibility of controlling these infections as an HIV prevention strategy; and the availability of low-cost diagnostics and treatments for these infections, the concept of treating and preventing sexually transmitted infections as a possible tool in HIV prevention remains an important one.[3, 22, 25]

Increasing evidence also links other infections (such as parasitic worm infections, TB, and malaria) with increased susceptibility to HIV infection or accelerated progression of HIV disease.[26] These infections also may increase the risk of HIV transmission by chronically activating the immune system, which results in increased viral replication and levels of HIV. Treatment of these co-infections—and, ultimately, the development and use of vaccines to prevent them—would be inherently beneficial to the patient and may be a useful HIV prevention modality.

■ **HIV vaccines.** Historically, vaccines have provided a safe, cost-effective, and efficient means of preventing illness, disability, and death as a result of a wide range of infectious diseases. Successful vaccines are usually based on the assumption that the body can mount an effective immune response during natural infection and that the vaccine will mimic the natural response to infection. With most vaccine-preventable diseases (for example, smallpox, polio, measles, and influenza), despite variable degrees of illness and death associated with infection, the body ultimately clears the infectious agent in the vast majority of patients, and the host is protected from infection upon future exposure to the pathogen in question. In essence, the body provides the proof of concept that it is capable of mounting an adequate immune response against natural infection. This proof of concept provides a high probability that a protective vaccine can be developed against the pathogen.

HIV, however, presents unique and significant scientific obstacles that have made the development of an HIV vaccine particularly daunting.[27, 28] Most important, in the vast majority of cases, the human host is unable to mount an effective immune response that clears HIV infection. In accordance with this sobering fact, there have been no documented instances of any individual with established HIV infection whose immune system has completely cleared the virus from his or her body, despite tens of millions of infections throughout the world.

The likely explanation for this phenomenon is the ability of HIV to rapidly invade and hide in host cells and to elude detection by normal immune-system responses; its extraordinary capacity to mutate and evolve; and its destruction or disabling of critical immune-system cells. Thus, the body has not provided the proof of concept that a protective vaccine is possible. In addition, an ideal animal model also is lacking in which to test such a vaccine and potentially provide such proof.

Thus, bold new approaches must be pursued. There now is a broad consensus about the need for a renewed focus on studies that will answer basic questions about how the body responds to HIV and how the disease develops from there. There is hope that such research will provide the insights needed for the rational design of better vaccine candidates.[28] The fundamental task at hand is to determine—by understanding the underlying molecular structure of biological functioning as well as through studies in animals and humans—the precise immune responses that are needed to prevent or control HIV replication. Then it will be necessary to design and test experimental vaccines to determine if they can evoke these responses. Meanwhile, much remains to be learned from clinical trials of existing vaccine candidates.

An HIV vaccine that conforms to the classic paradigm of viral vaccines remains the goal. Such a vaccine would induce immune responses that prevented the establishment of HIV infection by clearing virus before latent viral reservoirs develop. The HIV vaccine field recently was encouraged by data from a large clinical trial in Thailand in which a two-stage HIV vaccine regimen demonstrated a modest (approximately 31 percent) level of efficacy in protecting against HIV infection. This finding, which reached statistical significance, gave the first signal from any human study that a protective vaccine for HIV may be possible.[29]

However, even a less-than-perfect vaccine that does not prevent infection could benefit both individual recipients and the at-risk community. By blunting the initial burst of viral levels in the blood and reducing virus levels overall, such a vaccine could prolong the disease-free period and also reduce transmission.[27] Despite setbacks in clinical trials, each of these approaches—a classical vaccine that prevents initial infection and a vaccine that reduces viral load—continue to be pursued in preclinical and clinical studies. We remain cautiously optimistic that a substantial increase in our understanding of the mechanisms of HIV infection and disease will pave the way for the design of an effective HIV vaccine.

The Challenge Of HIV In An Era Of Constrained Resources

An enormous gap exists between funds made available for HIV/AIDS services and the investment needed if the goal of universal access to HIV prevention and treatment is to be achieved.[30] The ongoing global economic slowdown and the ever-growing HIV-infected population will no doubt widen the gap between resources and needs. New sources of revenue for the global HIV/AIDS fight are

needed, including investments by rich and middle-income countries whose contributions have so far been limited.

To "stretch" existing resources, proven interventions must be delivered in the most cost-effective manner consistent with favorable outcomes, such as using simple treatments overseen by community health care workers when appropriate. Evidence-based HIV interventions with broad coverage and takeup, which are intense and long-lasting, are needed if they are to have a major public health impact.

The HIV research enterprise has benefited immeasurably from the substantial funding it has received, without which the rapid advances made in understanding HIV/AIDS and developing new interventions would not have been possible. Budget figures of the U.S. National Institutes of Health (NIH), the world's largest funder of HIV/AIDS research, are illustrative of the extraordinary financial commitment to this field. Cumulative NIH funding for HIV/AIDS-related research totals about $42 billion from 1982 through fiscal year 2009. NIH AIDS research funding in fiscal year 1987 was about $294 million; by fiscal year 2009 that figure had grown more than tenfold to approximately $3.0 billion.[31, 32]

Spending on HIV/AIDS research by other agencies in the public, commercial, and private philanthropic sectors also has been substantial, especially in some of the key areas discussed in this paper.[33, 34] For example, in 2008 the total global investment in preventive HIV vaccine research and development was about US$868 million; for microbicide development, about US$244 million; and for other new prevention options, including pre-exposure prophylaxis and HSV-2 suppression, US$81 million.[33] In each of these areas, the overall trend has been one of increasing investment over the past few years.

In a time of fiscal constraint, we cannot expect that the growth in HIV/AIDS funding in the twenty-two years between 2009 and 2031 will approach that seen in the previous twenty-two years. However, public-sector, commercial, and philanthropic research funding in each of the areas discussed above must continue to increase substantially to ensure that new prevention and treatment options are developed and that positive research findings are translated into effective public health policies and programs.

Amid a global pandemic that shows few signs of abating, interventions added to our existing armamentarium and likely to be used in combination with existing tools are needed for controlling the HIV pandemic. We are faced with compelling scientific challenges to develop truly transforming interventions such as a cure for HIV infection and powerful new prevention modalities. Without these interventions, the scope and burden of the HIV pandemic will continue to grow. The goals described in this paper are ambitious but essential. They will require sustained support of a robust HIV/AIDS research agenda.

NOTES

1. A map showing the spread of the pandemic is available online at http://content.healthaffairs.org/cgi/content/full/28/6/1629/DC1.
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